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The prognosis of dementia with Lewy bodies

Author's accepted manuscript

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Summary

Dementia with Lewy bodies (DLB) is the second most common form of neurodegenerative dementia and is distinct from Alzheimer's disease (AD) in symptomatology and pathology. Yet little is known about its prognosis and disease trajectories. These issues are critical to informing clinical practice and research. The literature indicates a less favourable prognosis in DLB, with reported accelerated cognitive decline, shorter lifespan and increased nursing home admission. Healthcare costs are also reported to be higher in DLB than AD. Importantly, caregiver burden is significantly higher in DLB. It is likely that causative factors in these issues include the higher prevalence, and earlier emergence, of neuropsychiatric symptoms in DLB and the challenge of accurate diagnosis. Evidence concerning quality of life and hospital admissions is extremely limited despite the importance of these issues.

Key words: Dementia with Lewy bodies, prognosis, cognitive decline, survival, mortality, nursing home admission, hospitalisation, quality of life, caregiver burden, costs.

Introduction

Prognosis following a dementia diagnosis varies widely between individuals, and impacts considerably on the healthcare needs and future of each patient. Dementia is a progressive neurodegenerative condition. In its broadest sense, prognosis following a diagnosis of dementia includes a shortened life span, high levels of disability and complex care needs, leading to loss of independence and quality of life and eventual death. However, there are indications that different subtypes of dementia are likely to be associated with differing prognoses. Evaluations of prognostic factors to date have largely focused on either the dementia syndrome overall or Alzheimer's Disease (AD), the most common cause of dementia^{1,2}. It is important to elucidate how different dementia types impact on long-term health and service use in order to support individuals, physicians and healthcare services in managing a diagnosis of dementia. This issue is also key for wider societal planning for supporting people with dementia in the community.

Dementia with Lewy bodies (DLB) is the second most common form of neurodegenerative dementia in people over 65. DLB accounts for 10-20% of dementia cases, and thus contributes substantially to the overall impact of dementia³. DLB is pathologically and clinically distinct from AD and other forms of dementia. Pathologically, DLB is characterized by the presence of Lewy bodies - intraneuronal inclusions consisting mainly of alpha-synuclein aggregates and ubiquitin - in the neocortex, forebrain, brain stem and other parts of the nervous system. Most DLB patients also have AD-type changes, in particular amyloid plaques. Cognitive

symptoms typically present as difficulties with visuospatial domains and executive function rather than memory. Psychiatric and behavioural features, especially hallucinations, sleep disturbances and apathy, are more common and frequently present early in the disease course^{2,4-6}. In addition, other symptoms such as motor symptoms including falls, autonomic dysfunction, and fluctuating consciousness represent a challenge for patients, carers and the health-care system. Finally, these patients have a high risk of severe sensitivity reactions to antipsychotic drugs⁴. Despite these key differences in symptomatology and pathology, the evidence pertaining to DLB as a distinct condition is limited. This lack of clarity regarding DLB as a distinct condition is also reflected in the history of its clinical characterisation, which was hampered by conflicting evidence and complex case reports. Pivotal early research by Kosaka and colleagues emphasized the importance of cortical Lewy pathology as a substrate of dementia and began to define the core syndrome⁷. Subsequent work lead to operationalized criteria^{4,8} and in 2013 DLB was included Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as "Major or Mild Neurocognitive Disorder with Lewy Bodies"⁹. The current consortium criteria⁴ were largely followed, but the suggestive imaging feature omitted. In the the International Classification of Diseases, 11th Revision (ICD-11), bound to be published this year, is likely to also acknowledge DLB as a separate entity.

There are very few randomised controlled trials of treatments in DLB and the evidence relating to prognosis following a diagnosis has not been fully evaluated. Prognosis in dementia with Lewy bodies is an area of growing research interest. Early studies relied on post-mortem analyses, which were hindered by small sample sizes and selection bias towards younger patients with atypical features or uncertain diagnosis. The advent of a revised consensus criteria for DLB⁴ and advances in imaging and other

biomarkers have improved diagnostic rates and paved the way for larger scale longitudinal studies^{6,10}. The available evidence indicates that prognosis of DLB is highly variable and divergent from AD¹¹.

This review aims to present and interpret the current evidence in DLB regarding key prognostic measures including cognitive decline, mortality, institutionalisation and hospitalisation, costs, quality of life, and caregiver burden. The review is intended to provide an update on the likely trajectory and key issues following a diagnosis of DLB, and recommendations for physicians working with these patients.

Cognitive decline

Cognitive decline is inherent in all dementias but there is evidence suggesting that the speed and nature of decline in DLB may be distinct from AD. The direction and significance of any differences is not yet fully clear. Although quantification of fluctuations in attentional performance has been demonstrated to be a sensitive means of discriminating DLB from other dementias¹², this may contribute to the inconsistent findings in cognitive testing, in particular due to the small sample sizes in these studies. Taken as a whole, the literature is conflicting although recent large studies have provided important new data. Of 20 published studies seven have reported an accelerated cognitive decline in DLB (Table 1). The largest of these included cognitive decline data for up to three years on 800 DLB patients who had been seen at more than 20 international centres. A more rapid average annual decline in MMSE score (2.1 MMSE score points per year in DLB) compared to people with AD (1.63 points per year; $p=0.07$) and Parkinson's Disease Dementia (1.75 points per year; $p=0.19$) was observed. This difference reached significance when baseline

MMSE score was accounted for¹⁰. A further recent five-year prospective cohort study including 67 DLB cases also reported a faster annual decline in DLB than in AD (4.4 vs. 3.2 MSSE score points) with patients reaching a severe dementia state five months earlier than those with AD¹³. These two recent studies provide valuable large-scale and long-term data in the field, although it should be noted that the large study was based on retrospective data from different centres, and survival of participants in the prospective cohort study was low. The work concurs with early research in the field but conflicts with a previous meta-analysis of six small studies that found no difference in cognitive decline in DLB and AD¹⁴. This highlights the importance of prospective, larger, longer-term studies to examine the likely cognitive trajectory of DLB cases. The MMSE is a broad brush approach to cognitive assessment, and there is a need to consider individual cognitive domains to fully elucidate trends of cognitive decline in DLB. The Montreal Cognitive Assessment (MoCA)¹⁵, includes more executive and visuospatial features than the MMSE and has been demonstrated to have better sensitivity in both AD, DLB and PD^{16,17}. However, the sensitivity to change in DLB has been reported to be similar in MoCA and MMSE¹⁸. However, subdomain-specific cognitive decline has rarely been assessed in DLB. The literature indicates that verbal fluency deteriorates faster in DLB than in AD¹⁹ and that memory, recognition and recall decline more slowly^{20,21}. Prospective studies of cognitive domains are thus needed.

There is an emerging consensus for the role of concurrent pathologies in accelerated cognitive decline in DLB, indicating a possible continuum of trajectories dependent on underlying pathology. Several studies have shown faster deterioration in DLB cases with co-morbid AD pathology as assessed through post-mortem analyses of amyloid-beta ($A\beta$) burden²²⁻²⁴. A typical AD cerebrospinal fluid (CSF) profile, defined as low

$A\beta$ 42 alone or in combination with elevated tau and phosphorylated tau, have been shown to be significantly associated with a more rapid cognitive decline in DLB patients²⁵ (Figure 1), similar to findings in PD²⁶. Interestingly, CSF changes related to AD have been linked to worse performance in MMSE subtests assessing temporal lobe function (memory and orientation scores) in DLB, indicating a role for specific pathology in sub-domain declines²⁷. Further the presence of at least one apolipoprotein E4 allele has also been linked to a faster cognitive deterioration^{28,29}. Taken together, this evidence begins to suggest that cognitive decline in DLB is likely to be dictated in part by concurrent AD pathology, leading to a spectrum of possible outcomes dependent on the individual pathological status. It is also likely that co-morbid AD pathology leads to heterogeneity in DLB research cohorts, and may account for the large variation reported in DLB studies. Thus, although CSF does not aid in the diagnosis of DLB due to its overlap with AD³⁰, physicians may find that CSF analyses provide prognostic information for individual cases. However, before this can be operationalised further CSF and imaging studies of amyloid and tau pathologies in DLB and concurrent cognitive decline are warranted.

Longevity and mortality

Survival of individual patients following a diagnosis of DLB is difficult to predict, particularly due to the frailties and co-morbidities that are common in older adults and which contribute to a complex risk profile for mortality. The literature shows good agreement on key risk factors for earlier mortality, which include male gender, higher age at onset, larger burden of co-morbid conditions, and functional impairment³¹⁻³³. These factors are shared with AD and can be considered to be generic mortality risks

across the dementia spectrum. A number of DLB specific predictors of shorter survival have also been defined (Figure 2). These include gait abnormalities, fluctuating cognition and hallucinations early in the disease course. Use of antipsychotics may increase mortality in people with dementia³⁴, and this is particularly relevant for DLB given the high proportion with psychosis and the risk for severe hypersensitivity reactions to antipsychotics. There are inconsistencies in the evidence base regarding the associated risk with extrapyramidal symptoms, with one study reporting a protective effect of when a tremor is present^{31,32}.

In terms of autonomic dysfunction, orthostatic hypotension is associated with higher mortality in DLB patients, but constipation and urinary incontinence are not³⁵. Noradrenergic cardiac denervation is a well-known feature of DLB. However, low cardiac MIBG uptake is not necessarily correlated with actual symptoms of autonomic dysfunction^{36,37}. Parkinson's disease has been linked to higher mortality due to cardiovascular events³⁸ and prolonged QTc on electrocardiography³⁹. These findings could be applicable to DLB, although the latter could not be replicated in a DLB sample⁴⁰. More studies are needed to explore this.

Autopsy studies have attempted to define survival in people with DLB, with estimates ranging from 1.8 to 9.5 years^{41,42}. A meta-analysis of 150 neuropathologically confirmed cases of DLB showed a mean survival time after diagnosis of 6.1 years¹¹. However, these figures are based on small sample sizes and so should be treated with caution. Of interest with regard to treatment decisions, one randomized placebo-controlled trial of the glutamate inhibitor memantine in DLB and PDD patients showed a positive impact on survival⁴³. Although this evidence is too weak to be the basis of treatment decision-making this finding does indicate the potential role of this treatment

approach in DLB and may warrant further investigation to establish the underlying mechanism for improved survival. Unfortunately, very few clinical trials in DLB have been reported, but a number are ongoing and it will be important to explore the role of novel treatments in long-term prognosis and survival.

When considering differential survival times from diagnosis between DLB and AD there is an added complexity due to the challenge of obtaining an accurate DLB diagnosis, which increases the likelihood of a DLB diagnosis being made relatively later in the dementia 'journey' than for people with AD. Nine studies have examined this question, of which six report a shorter survival time in DLB compared with AD, whereas the remaining three showed no difference. (Table 1). Studies have defined survival in two ways, either from onset of disease, or from diagnosis. Survival estimates range between 5.5 and 7.7 years, and between 1.9 and 6.3 years respectively for these two definitions^{22,27,32,44-46}. To mitigate potential inaccuracies due to recall bias of duration and delay in diagnosis, Stubendorff and colleagues⁴⁵ measured survival from fixed MMSE score points (20±1 and 17±1), demonstrating worse survival in DLB than in AD patients.

As with cognitive decline, co-morbid AD pathology and its biomarkers are associated with shorter survival in DLB. Target biomarkers include the apolipoprotein E4 allele, lower hippocampal volume and a high level of CSF t-tau⁴⁷⁻⁴⁹. This evidence adds weight to the theory that concurrent DLB and AD pathology lead to a less favourable prognosis in DLB.

Nursing home admission

Nursing home admission is an important indicator of disease progression. A move to permanent residential care is associated with complex and full time care needs and loss of independence. Importantly for healthcare services, residential care contributes to a vastly increased cost of care^{50,51}. Factors that contribute to the risk of nursing home admission in dementia are older age, poorer cognitive and functional state, living alone and caregiver burden. A major trigger for institutionalisation is neuropsychiatric symptoms such as aggression and psychosis⁵², as well as motor symptoms which contribute to further disability.

Since DLB is closely connected with hallucinations and behavioural symptoms it might be expected that these patients are more likely to be placed in a nursing home earlier than their AD counterparts. Indeed, figures for respite care placement from cross-sectional economic studies indicate that DLB patients spent at least three times the number of days per year in nursing care facilities than AD patients^{51,53}. However, literature pertaining to long-term placement is limited and conflicting (Table 1). One Scandinavian study reported that median time from mild dementia to entry into nursing homes was 1.8 years in DLB patients, which is two years shorter than in AD⁵⁴. Contributing factors are male gender and antipsychotic prescriptions, which indicates that neuropsychiatric symptoms are a likely common trigger. Acetylcholinesterase inhibitors appear to be protective⁵⁴, which underscore that cholinergic deficits are a particular prominent feature in DLB⁵⁵.

In contrast, two further studies in the US and Japan reported no difference in nursing home admission between DLB and other dementia groups^{32,56}, despite one study

reporting that DLB patients reached a composite endpoint (nursing home admission, hospitalisation or death) on average one year earlier than AD patients.

Hospitalisation

Admission to general hospital is a critical event for both patient and healthcare services. Similarly to nursing home placements, hospitalisation triggers a high cost profile for care and often leads to longer term placement in residential care. For people with dementia hospitalisation is undesirable as it is associated with a worsening of cognition and the emergence or worsening of neuropsychiatric symptoms, which are often managed with antipsychotic medications⁵⁷. An additional risk in people with DLB is the misdiagnosis and mismanagement of delirium⁵⁸. DLB typically presents with visual hallucinations and fluctuating attention and cognition⁴. This is similar to, and easily misinterpreted as, a hyperactive delirium or acute confusional state. One common pitfall lies in misdiagnosing DLB as delirium. Another is missing an acute underlying medical condition due to the assumption that symptoms are part of the DLB state. The first may lead to patients being treated with antipsychotics, with substantial risk of severe reactions and mortality. The later might cause inadequate investigation management of common causes of delirium as pain or potentially life-threatening conditions⁵⁷⁻⁵⁹.

However, there is also evidence that delirium occurs particularly often in DLB, more so than in AD, and may even be a presenting symptom^{59,60}. In one study 25% of DLB patients had an episode of delirium prior to dementia onset so it may be expected that DLB patients are more at risk of hospitalisation than other dementia types. Thus, clinicians should consider DLB as a possible differential diagnosis in patients admitted

with delirium. If there is a suspicion of DLB underlying a delirious episode, established DLB biomarkers as DaT scan or SPECT⁴ might be helpful to clarify diagnosis once the episode has resolved⁵⁸.

Studies examining rates of hospitalisation after diagnosis of DLB are scarce and sample sizes are small, so interpretation of the literature is difficult. Of three studies, two report a higher hospitalisation rate in DLB compared with AD, but a third study reported the opposite^{51,53,56} (Table 1). Importantly, the most common reasons for hospitalisation are falls and bronchopneumonia. These are recognised as the highest risk factors for hospital admissions across the wider frail older adult group, so this indicates that the general advice for falls prevention and prompt treatment for respiratory infection is directly applicable to DLB.

Healthcare costs

Dementia has a high economic impact on society and health care costs increase as the illness progresses and functional abilities decline. Progression to severe dementia and admission to nursing homes are particularly cost-intensive^{61,62}, and there are a number of established predictors for increased cost, including living alone, functional decline and co-morbidity. Economic evaluations in dementia are complex, yet they provide essential information to enable decision-making in healthcare policy and to dictate service provision.

Four studies have examined the relative costs of DLB and AD, of which three report a higher cost with DLB (Table 1, Figure 3). Higher costs are attributed to increased, or

longer-term, use of high-cost accommodation such as nursing homes, increased pharmacotherapy and higher utilisation of outpatient care, community services and informal help^{51,53}. Given the apparent increased risk of hospital and nursing home admission, these findings are not unexpected. There also appears to be a differential in the type of support used by people with DLB and AD, with DLB patients using more assistive devices and incurring higher indirect costs through informal care giving, while AD patients rely more on home-based healthcare⁶³. Interestingly, one study suggests that costs in DLB may not be as strongly determined by cognitive decline as in AD. This is likely due to the higher prevalence and earlier onset of neuropsychiatric symptoms, parkinsonism and other motor symptoms which may predominate in the cost impact of DLB. As with nursing home admission, cost savings are made when acetylcholinesterase inhibitors (AChEIs) are prescribed in the first year after diagnosis⁶⁴. Again, this evidence could be interpreted as an indication of a close relationship between institutionalization and cost of care.

Quality of life

Quality of life (QoL) is increasingly considered to be the most meaningful outcome measure for people with dementia. It is conceptually challenging, particularly when working with groups who have limited capacity for self-report and insight into their condition and day-to-day experience, but is a critical aspect of both research output and clinical practice⁶⁵. In standardised scales QoL is consistently rated higher by patients than by caregiver proxy-measures. This is likely due to the disconnect caused by cognitive impairment, and enhanced by caregiver stress and burden^{66,67}.

QoL has not been fully defined in DLB, and very few trials have included it as an outcome. The limited literature suggests that both patient- and proxy-rated QoL is lower in people with DLB compared with AD⁶⁸, with one study reporting 25% and 6% of people falling below acceptable thresholds on the EQ-5D, respectively^{69,70} (Table 1). There are a number of strong candidate determinants for QoL in DLB. Causative factors for lower QoL include higher frequency of neuropsychiatric symptoms such as depression, apathy and hallucinations, in addition to the high dependency states and restrictions in living arrangements seen in DLB. In line with trends seen across the dementia spectrum, cognitive function does not correlate with QoL⁶⁵. Interestingly, one RCT of memantine reported a significant benefit to QoL in people with DLB and PDD, which was also associated with improvements in subdomains related to body function, physical health, energy, mood, and memory⁷¹. Demonstrating improvement of QoL in clinical trials is difficult but remains a priority in DLB trials.

Caregiver burden

DLB might be predicted to associate strongly with caregiver burden due to the specific spectrum of non-cognitive symptoms that impact directly on caregivers, including psychosis, behavioural symptoms such as aggression and agitation, and night-time behaviours including wandering. These aspects of dementia, which are particularly common in DLB, are correlated with increased levels of caregiver distress and burden, and are a frequently named trigger for institutionalisation across all types of dementia^{72,73}. There is considerable literature describing this correlation in DLB groups^{2,74-76}, with particular emphasis on anxiety, apathy, delusions and hallucinations^{2,75}. A small number of studies report higher levels of caregiver burden

in DLB compared with AD, particularly due to the challenge of managing behavioural symptoms⁷⁴ (Table 1). Of note, psychiatric symptoms are also related to a variety of parasomnias which are particularly common in DLB, and thus likely also contribute to carer burden^{54,77}. The literature includes a large cross-sectional survey of carers conducted by the Lewy Body Dementia Association, which highlighted the role of Activities of Daily Living as a potentially major factor in caregiver burden. Carers reported that over 90% of LBD patients were unable to perform complex tasks and over 60% needed support with basic activities of daily living⁷⁸. This is in agreement with other studies, and implies that motor symptoms also contribute, although there is a lack of agreement regarding the scale of impact of functional impairment^{75,76}. Thus, clinicians need to carefully consider depression and exhaustion in those caring for people with DLB, as well as their need for information and support. In a UK survey largely completed by spouses or first degree relatives, the support need most frequently identified related to hallucinations. The importance of explaining what Lewy body disease is, its pathophysiology and the impact on the brain and body as a whole was highlighted⁷⁹.

Recommendations

There are varying levels of evidence supporting different aspects of prognosis for DLB, and much of the literature is drawn from small, single-centre studies. An inherent challenge in DLB research is the issue of diagnostic accuracy, differentiating DLB from AD and from Parkinson's disease dementia, and the lack of pathological confirmation of diagnosis in addition to the lack of clarity around disease trajectory in these patients, although dopamine transporter SPECT and other biomarkers may help in addition to

actively applying the diagnostic criteria. Despite this, the literature leads to a number of conclusions that are evidence-based.

There is a clear message that DLB carries a poorer prognosis, defined as increased cost profile, accelerated nursing home admission and shorter time to death. Key questions that remain relate to the elucidation of which clinical and pathological features contribute to these poorer outcomes and which are the biggest priority as targets for intervention. Motor symptoms, cognitive decline and neuropsychiatric symptoms are all likely to contribute in some way, but we would suggest that the particularly high frequency of neuropsychiatric symptom in these individuals, such as psychosis and depression, highlights these as particularly important treatment targets.

Although the existing data is less clear-cut there is also a suggestion of accelerated cognitive decline, greater caregiver burden and possibly a greater impact on quality of life in DLB patients. These should be taken into account by physicians when considering long-term support, treatment and care (Figure 4).

Although DLB is the second most common form of neurodegenerative dementia, it has received only a fraction of the research investment and focus. There are currently no licensed therapies for cognition or neuropsychiatric symptoms in Europe, no established evidence-based non-pharmacological interventions and a paucity of new intervention studies. The poor prognosis and high personal and financial cost make new treatments studies in DLB an urgent priority.

Conclusions and future perspectives

Research on prognosis in dementia with Lewy bodies indicates important differences in disease trajectories and prognosis compared to other forms of dementia, suggesting that key prognostic features such as survival and cognitive decline are less favourable in DLB than in AD. Accordingly, these patients need specialized care and more frequent monitoring. Despite this, there are few studies on key outcomes, and no licensed therapies. Analysis of the quality of studies published to date shows a lack of high quality design, which limits the interpretation that can be made from much of literature at present (Table 1). This underlines the importance of larger scale studies on prognosis in DLB, in which multinational research co-operations or electronic health record databases could play an important role. The existing evidence also underlines the need for well-defined DLB cohorts, potentially through a combination of neuroimaging, genetic profiling and biomarker analysis, to reduce heterogeneity in clinical trials.

Search strategy and selection criteria

This review was informed by a systematic literature search performed on 1st August 2016. The electronic database PubMed was searched for articles published between 1st January 1990 and 31st July 2016 with the search terms “Lewy body OR Lewy bodies OR DLB OR LBD” and “cognition OR cognitive decline OR survival OR mortality OR nursing home admission OR hospitalization OR cost OR quality of life OR QOL OR carer OR caregiver”. References from the identified articles were also scrutinised for relevant studies. There were no language restrictions. Articles were selected through author consensus with a focus on longitudinal studies. Studies were scored for quality using a system based on a previous review ¹⁴. Maximum score was 6 and based on two subscales: number DLB participants at baseline (more than 90 = 3, 61-90 = 2, 31-60 = 1, 30 or less = 0) and the follow-up time (more than 3 years = 3, up to 3 years = 2, up to 2 years = 1, 1 year or less = 0). To illustrate differences between the included studies we devised a traffic light system (5-6 = green; 3-4 = yellow; 2 or less = red).

Contributors

DA and CM proposed the topic for this Review. All authors contributed equally to preparation and review of the manuscript, and approved the version submitted to the journal.

Declarations of interest

CB reports grants and personal fees from Lundbeck and Acadia, and personal fees from Roche, Orion, GSK, Otusaka, Heptares, and Lilly outside the submitted work.


DA has received grants from GE Healthcare, and personal fees from Novartis and H Lundbeck outside the submitted work.

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Table 1: Summary of studies comparing outcomes and quality of key prognostic factors between DLB and AD

The traffic light system illustrates study quality. A maximum score of 6 calculated from two subscales (number DLB participants at baseline: more than 90 = 3, 61-90 = 2, 31-60 = 1, 30 or less = 0; and follow-up time: more than 3 years = 3, up to 3 years = 2, up to 2 years = 1, 1 year or less = 0) translates into the following colouring: Green indicates score 5-6, yellow 3-4, red 2 or less. Details of the included studies are presented in the Appendix.

	Number of studies	Number of patients included	Number of studies with worse outcome in DLB	Number of studies showing no difference	Number of studies with worse outcome in AD	Study Quality	Impact of the outcome	Future research directions
Cognition	20	1751 AD / 1607 (DLB or AD/DLB)	7 2 DLB faster than AD; 1 DLB faster than AD if poor visuospatial skills impaired at baseline; 1 DLB faster in verbal fluency; 1 DLB faster when MMSE score used as	11	2 1 AD faster in delayed recall; 1 AD faster on recognition		<ul style="list-style-type: none"> • Cognitive decline at least as rapid as in AD • Possibly following a different pattern than AD, which composite cognitive scores might not be able to detect • Co-morbid AD seems to predict faster decline 	<ul style="list-style-type: none"> • Subdomain specific decline needed as current memory tests do not capture executive and visuospatial decline accurately (MoCA needs further evaluation as potential tool) • AD patients with symptoms suggestive of DLB might need more intense diagnostic to identify co-morbid DLB as this has substantial impact on prognosis

			baseline co- variate; 2 AD/DLB faster than AD (and faster than pure DLB)					
Survival	9	1656 AD / 418 DLB	6 (4 from dx; 2 from disease onset)	3	-	1 8	<ul style="list-style-type: none"> • Age of onset appears to be similar in AD and DLB • Survival seems to be shorter in DLB • Survival time in DLB varies between 1.9 to 6.3 years after diagnosis • AD cohorts report 3.2 to 6.6 years after diagnosis 	
Nursing home admission	3	485 AD / 162 DLB	1	2	-	1 2	<ul style="list-style-type: none"> • Time to nursing home admission between 1.8 and 6.1 years in DLB • Nursing home admission occurs between 6 months and 1.8 years earlier in DLB than AD • Predictors: self-reported depressive symptoms, extrapyramidal signs, longer duration of symptoms, antipsychotic use, AChEI prescription (protective) 	<ul style="list-style-type: none"> • Due to high economic impact more research needed into factors predicting nursing home admission

Hospitalisation	3 (2 are cost analyses)	239 AD / 105 DLB	2	-	1	1 2	<ul style="list-style-type: none"> Economic analyses had contradictory results DLB patients had between 10.3 and 4.1 days of hospital care per year AD patients between 1.6 and 6.1 days of hospital care per year 	<ul style="list-style-type: none"> More research needed into burden of hospitalization in DLB As hospitalization is potentially more harmful for DLB than AD patients, more research needed into factors leading to hospitalization
Costs	4	371 AD / 98 DLB	3	1 (only community dwelling)	-	4	<ul style="list-style-type: none"> Cost in DLB about twice as high as in AD No difference if only community-dwelling patients Nursing home admission appears to major cost factor and cost difference factor 	<ul style="list-style-type: none"> Underlines importance of researching factors predicting nursing home admission in DLB
Quality of life	1	34 DLB / 34 AD (matched)	1	-	-	1	<ul style="list-style-type: none"> Indicates lower quality of life in DLB 24% in DLB / 6% of AD patients consider health state worth than death Neuropsychiatric symptoms, functional decline, and living arrangements predict lower QoL in DLB 	
Caregiver burden	4	282 AD / 143 DLB	4	-	-	4	<ul style="list-style-type: none"> Higher carer stress in DLB consistently reported Correlated with neuropsychiatric symptoms Differing results regarding correlation of functional difficulties and carers stress 	<ul style="list-style-type: none"> Highlights the need to find novel ways to address neuropsychiatric symptoms in DLB Further the link between factors influencing carers stress, and risk of residential placement warrant further investigation

Figure 1: The impact of an AD CSF profile on cognitive decline in DLB (from Abdelnour et al., 2016²⁵)

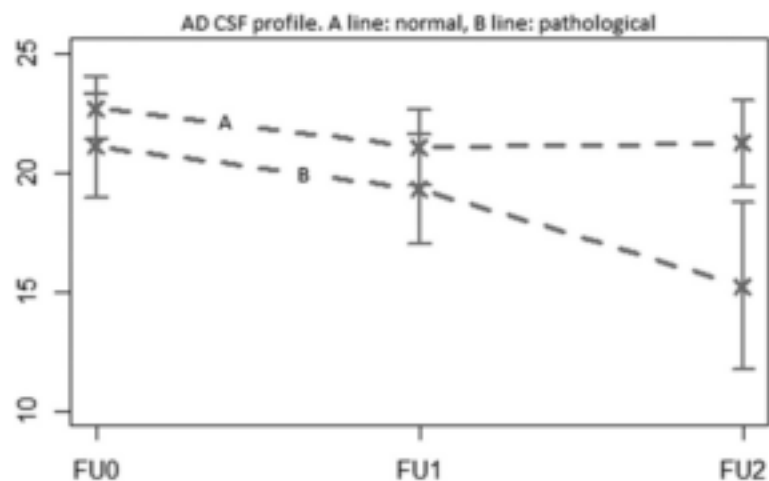


FIG. 1. Change in MMSE from baseline (FU0) to one (FU1) and two (FU2) years follow-up in those with ($n=32$, Line B) and without ($n=68$, Line A) a CSF AD profile. The difference was statistically significant (LME, $P=0.04$).

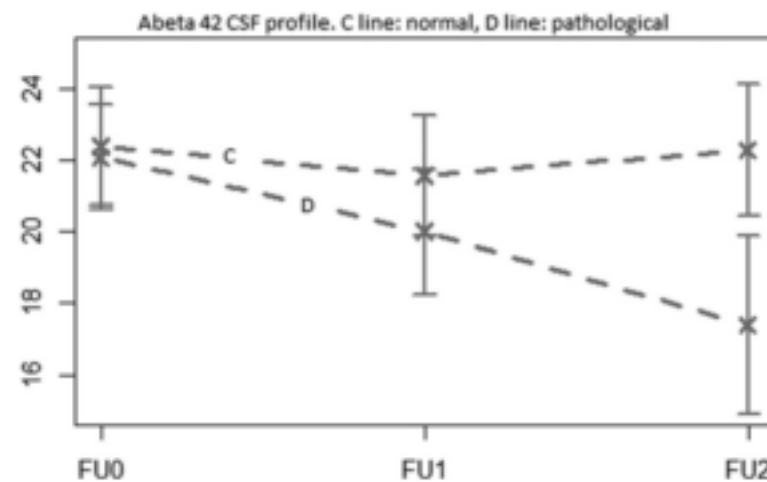


FIG. 2. Change in MMSE from baseline (FU0) to one (FU1) and two (FU2) years follow-up in those with ($n=69$, Line D) and without an abnormally low ($n=31$, Line C) CSF A β 42 value. The difference was statistically significant (LME, $P=0.0079$).

Figure 2: DLB-specific and general predictors of mortality

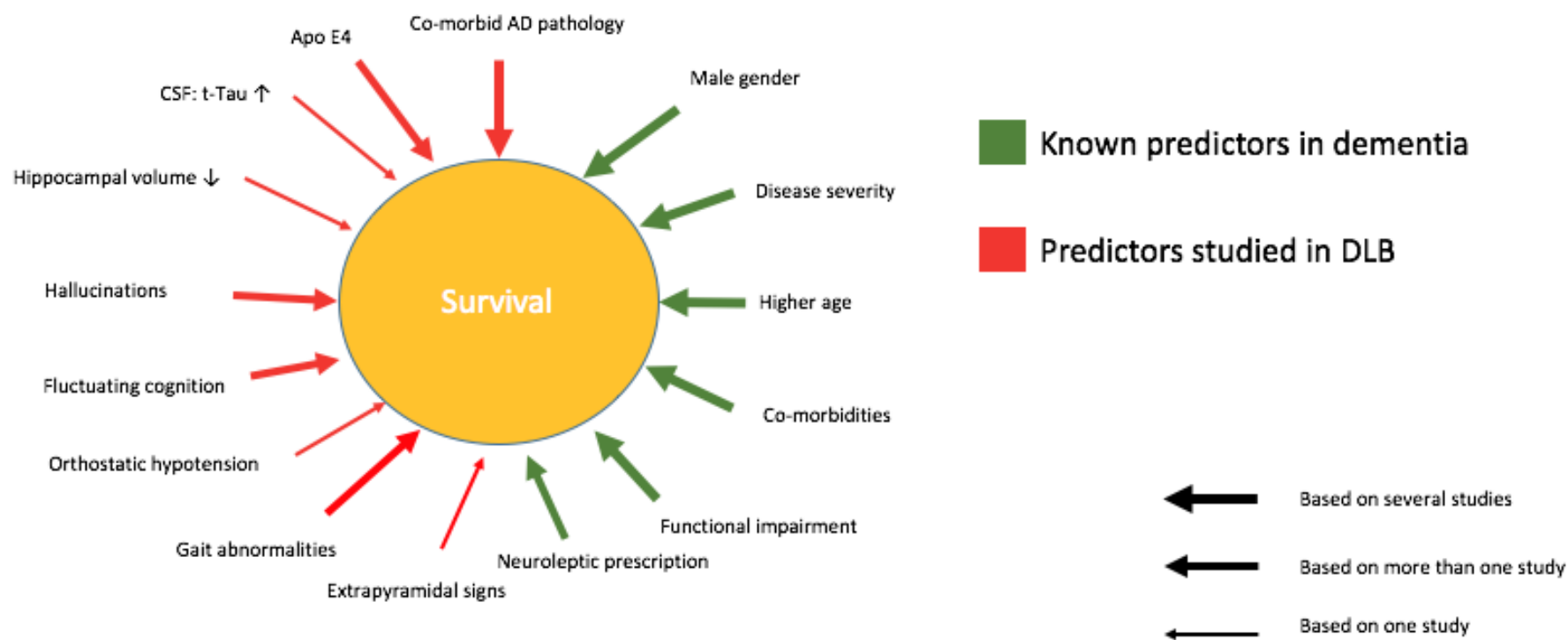


Figure 3: Mean costs by months of survival by diagnosis (from Vossius et al., 2016)⁶⁴

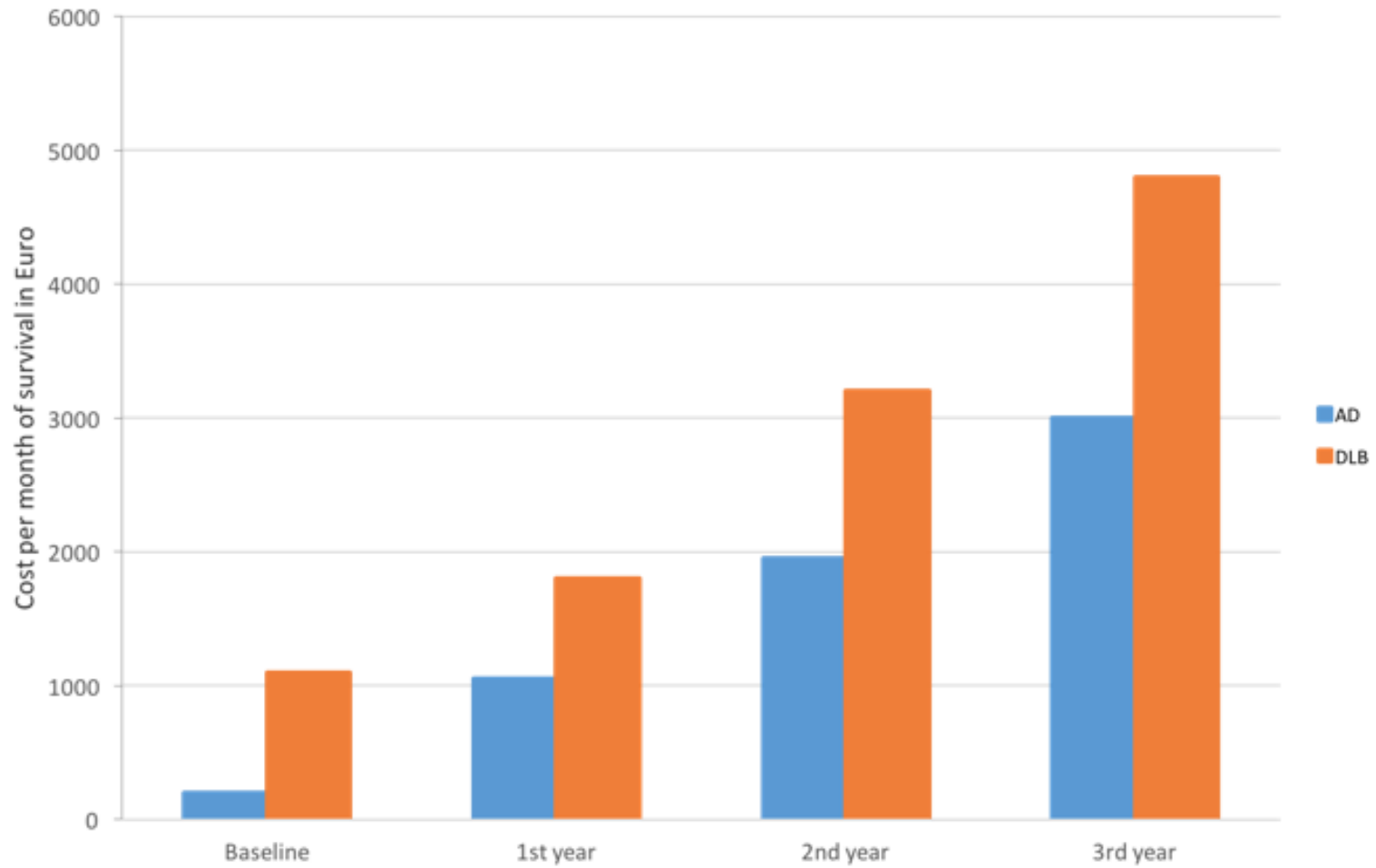
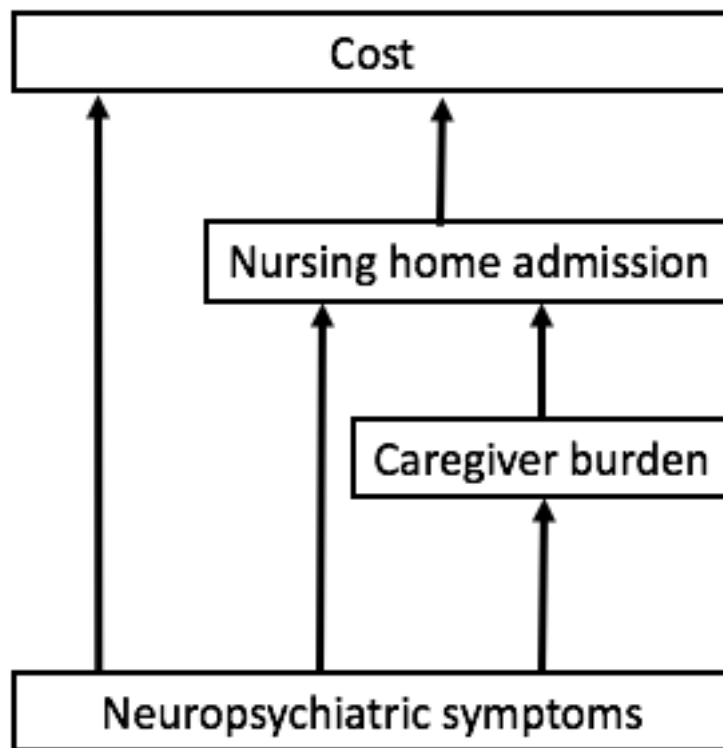


Figure 4: Model on neuropsychiatric symptoms as cost drivers in DLB



References:

1. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement* 2013; **9**(1): 63-75 e2.
2. Bjoerke-Bertheussen J, Ehrt U, Rongve A, Ballard C, Aarsland D. Neuropsychiatric symptoms in mild dementia with lewy bodies and Alzheimer's disease. *Dement Geriatr Cogn Disord* 2012; **34**(1): 1-6.
3. Zaccai J, McCracken C, Brayne C. A systematic review of prevalence and incidence studies of dementia with Lewy bodies. *Age Ageing* 2005; **34**(6): 561-6.
4. McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology* 2005; **65**(12): 1863-72.
5. Ferman TJ, Arvanitakis Z, Fujishiro H, et al. Pathology and temporal onset of visual hallucinations, misperceptions and family misidentification distinguishes dementia with Lewy bodies from Alzheimer's disease. *Parkinsonism Relat Disord* 2013; **19**(2): 227-31.
6. Walker Z, Possin KL, Boeve BF, Aarsland D. Lewy body dementias. *Lancet* 2015; **386**(10004): 1683-97.
7. Kosaka K, Oyanagi S, Matsushita M, Hori A. Presenile dementia with Alzheimer-, Pick- and Lewy-body changes. *Acta Neuropathol* 1976; **36**(3): 221-33.
8. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology* 1996; **47**(5): 1113-24.
9. Association AP. Diagnostic and statistical manual of mental disorders DSM-5. . 5th edn. ed. Washington, DC: American Psychiatric Association; 2013.
10. Kramberger MG OG, Lemstra AW, et al. Clinical characteristics and course of DLB: results from a large longitudinal multicentre cohort. . AAIC. Washington; 2015.
11. Cerci SP, Bylsma FW. Lewy bodies and progressive dementia: a critical review and meta-analysis. *J Int Neuropsychol Soc* 1997; **3**(2): 179-94.
12. Ballard CG, Aarsland D, McKeith I, et al. Fluctuations in attention: PD dementia vs DLB with parkinsonism. *Neurology* 2002; **59**(11): 1714-20.
13. Rongve A, Soennesyn H, Skogseth R, et al. Cognitive decline in dementia with Lewy bodies: a 5-year prospective cohort study. *BMJ Open* 2016; **6**(2): e010357.
14. Breitve MH, Chwiszczuk LJ, Hynninen MJ, et al. A systematic review of cognitive decline in dementia with Lewy bodies versus Alzheimer's disease. *Alzheimers Res Ther* 2014; **6**(5-8): 53.
15. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005; **53**(4): 695-9.
16. Lessig S, Nie D, Xu R, Corey-Bloom J. Changes on brief cognitive instruments over time in Parkinson's disease. *Mov Disord* 2012; **27**(9): 1125-8.
17. Wang CS, Pai MC, Chen PL, Hou NT, Chien PF, Huang YC. Montreal Cognitive Assessment and Mini-Mental State Examination performance in patients with mild-to-moderate dementia with Lewy bodies, Alzheimer's disease, and normal participants in Taiwan. *Int Psychogeriatr* 2013; **25**(11): 1839-48.
18. Biundo R, Weis L, Bostantjopoulou S, et al. MMSE and MoCA in Parkinson's disease and dementia with Lewy bodies: a multicenter 1-year follow-up study. *J Neural Transm (Vienna)* 2016; **123**(4): 431-8.

19. Ballard C, Patel A, Oyebode F, Wilcock G. Cognitive decline in patients with Alzheimer's disease, vascular dementia and senile dementia of Lewy body type. *Age Ageing* 1996; **25**(3): 209-13.
20. Stavitsky K, Brickman AM, Scarmeas N, et al. The progression of cognition, psychiatric symptoms, and functional abilities in dementia with Lewy bodies and Alzheimer disease. *Arch Neurol* 2006; **63**(10): 1450-6.
21. Heyman A, Fillenbaum GG, Gearing M, et al. Comparison of Lewy body variant of Alzheimer's disease with pure Alzheimer's disease: Consortium to Establish a Registry for Alzheimer's Disease, Part XIX. *Neurology* 1999; **52**(9): 1839-44.
22. Olichney JM, Galasko D, Salmon DP, et al. Cognitive decline is faster in Lewy body variant than in Alzheimer's disease. *Neurology* 1998; **51**(2): 351-7.
23. Nelson PT, Kryscio RJ, Jicha GA, et al. Relative preservation of MMSE scores in autopsy-proven dementia with Lewy bodies. *Neurology* 2009; **73**(14): 1127-33.
24. Kraybill ML, Larson EB, Tsuang DW, et al. Cognitive differences in dementia patients with autopsy-verified AD, Lewy body pathology, or both. *Neurology* 2005; **64**(12): 2069-73.
25. Abdelnour C, van Steenoven I, Londos E, et al. Alzheimer's disease cerebrospinal fluid biomarkers predict cognitive decline in lewy body dementia. *Mov Disord* 2016; **31**(8): 1203-8.
26. Alves G, Bronnick K, Aarsland D, et al. CSF amyloid-beta and tau proteins, and cognitive performance, in early and untreated Parkinson's disease: the Norwegian ParkWest study. *J Neurol Neurosurg Psychiatry* 2010; **81**(10): 1080-6.
27. Andersson M, Zetterberg H, Minthon L, Blennow K, Londos E. The cognitive profile and CSF biomarkers in dementia with Lewy bodies and Parkinson's disease dementia. *Int J Geriatr Psychiatry* 2011; **26**(1): 100-5.
28. Ballard C, O'Brien J, Morris CM, et al. The progression of cognitive impairment in dementia with Lewy bodies, vascular dementia and Alzheimer's disease. *Int J Geriatr Psychiatry* 2001; **16**(5): 499-503.
29. Vijayaraghavan S, Darreh-Shori T, Rongve A, et al. Association of Butyrylcholinesterase-K Allele and Apolipoprotein E varepsilon4 Allele with Cognitive Decline in Dementia with Lewy Bodies and Alzheimer's Disease. *J Alzheimers Dis* 2016; **50**(2): 567-76.
30. van Steenoven I, Aarsland D, Weintraub D, et al. Cerebrospinal Fluid Alzheimer's Disease Biomarkers Across the Spectrum of Lewy Body Diseases: Results from a Large Multicenter Cohort. *J Alzheimers Dis* 2016; **54**(1): 287-95.
31. Jellinger KA, Wenning GK, Seppi K. Predictors of survival in dementia with lewy bodies and Parkinson dementia. *Neurodegener Dis* 2007; **4**(6): 428-30.
32. Williams MM, Xiong C, Morris JC, Galvin JE. Survival and mortality differences between dementia with Lewy bodies vs Alzheimer disease. *Neurology* 2006; **67**(11): 1935-41.
33. Todd S, Barr S, Roberts M, Passmore AP. Survival in dementia and predictors of mortality: a review. *Int J Geriatr Psychiatry* 2013; **28**(11): 1109-24.
34. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA* 2005; **294**(15): 1934-43.
35. Stubendorff K, Aarsland D, Minthon L, Londos E. The impact of autonomic dysfunction on survival in patients with dementia with Lewy bodies and Parkinson's disease with dementia. *PLoS One* 2012; **7**(10): e45451.

36. Orimo S, Ozawa E, Nakade S, Sugimoto T, Mizusawa H. (123)I-metaiodobenzylguanidine myocardial scintigraphy in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1999; **67**(2): 189-94.
37. Matsui H, Nishinaka K, Oda M, Komatsu K, Kubori T, Udaka F. Does cardiac metaiodobenzylguanidine (MIBG) uptake in Parkinson's disease correlate with major autonomic symptoms? *Parkinsonism Relat Disord* 2006; **12**(5): 284-8.
38. Liang HW, Huang YP, Pan SL. Parkinson disease and risk of acute myocardial infarction: A population-based, propensity score-matched, longitudinal follow-up study. *Am Heart J* 2015; **169**(4): 508-14.
39. Oka H, Mochio S, Sato H, Katayama K. Prolongation of QTc interval in patients with Parkinson's disease. *Eur Neurol* 1997; **37**(3): 186-9.
40. Sonnesyn H, Nilsen DW, Rongve A, et al. High prevalence of orthostatic hypotension in mild dementia. *Dement Geriatr Cogn Disord* 2009; **28**(4): 307-13.
41. McKeith IG, Perry RH, Fairbairn AF, Jabeen S, Perry EK. Operational criteria for senile dementia of Lewy body type (SDLT). *Psychol Med* 1992; **22**(4): 911-22.
42. Klatka LA, Louis ED, Schiffer RB. Psychiatric features in diffuse Lewy body disease: a clinicopathologic study using Alzheimer's disease and Parkinson's disease comparison groups. *Neurology* 1996; **47**(5): 1148-52.
43. Stubendorff K, Larsson V, Ballard C, Minthon L, Aarsland D, Londos E. Treatment effect of memantine on survival in dementia with Lewy bodies and Parkinson's disease with dementia: a prospective study. *BMJ Open* 2014; **4**(7): e005158.
44. Oesterhus R, Soennesyn H, Rongve A, Ballard C, Aarsland D, Vossius C. Long-term mortality in a cohort of home-dwelling elderly with mild Alzheimer's disease and Lewy body dementia. *Dement Geriatr Cogn Disord* 2014; **38**(3-4): 161-9.
45. Stubendorff K, Hansson O, Minthon L, Londos E. Differences in survival between patients with dementia with Lewy bodies and patients with Alzheimer's disease--measured from a fixed cognitive level. *Dement Geriatr Cogn Disord* 2011; **32**(6): 408-16.
46. Magierski R, Kłoszewska I, Sobów TM. The influence of vascular risk factors on the survival rate of patients with dementia with Lewy bodies and Alzheimer disease. *Neurologia i Neurochirurgia Polska* 2010; **44**(2): 139-47.
47. Graff-Radford J, Lesnick TG, Boeve BF, et al. Predicting Survival in Dementia With Lewy Bodies With Hippocampal Volumetry. *Mov Disord* 2016; **31**(7): 989-94.
48. Bostrom F, Hansson O, Blennow K, et al. Cerebrospinal fluid total tau is associated with shorter survival in dementia with Lewy bodies. *Dement Geriatr Cogn Disord* 2009; **28**(4): 314-9.
49. Wakisaka Y, Furuta A, Tanizaki Y, Kiyohara Y, Iida M, Iwaki T. Age-associated prevalence and risk factors of Lewy body pathology in a general population: the Hisayama study. *Acta Neuropathol* 2003; **106**(4): 374-82.
50. Bharucha AJ, Pandav R, Shen C, Dodge HH, Ganguli M. Predictors of nursing facility admission: a 12-year epidemiological study in the United States. *J Am Geriatr Soc* 2004; **52**(3): 434-9.
51. Bostrom F, Jonsson L, Minthon L, Londos E. Patients with Lewy body dementia use more resources than those with Alzheimer's disease. *Int J Geriatr Psychiatry* 2007; **22**(8): 713-9.
52. Gaugler JE, Yu F, Krichbaum K, Wyman JF. Predictors of nursing home admission for persons with dementia. *Med Care* 2009; **47**(2): 191-8.

53. Murman DL, Kuo SB, Powell MC, Colenda CC. The impact of parkinsonism on costs of care in patients with AD and dementia with Lewy bodies. *Neurology* 2003; **61**(7): 944-9.
54. Rongve A, Vossius C, Nore S, Testad I, Aarsland D. Time until nursing home admission in people with mild dementia: comparison of dementia with Lewy bodies and Alzheimer's dementia. *Int J Geriatr Psychiatry* 2014; **29**(4): 392-8.
55. Mori E, Ikeda M, Kosaka K, Donepezil DLBSI. Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled trial. *Ann Neurol* 2012; **72**(1): 41-52.
56. Hanyu H, Sato T, Hirao K, Kanetaka H, Sakurai H, Iwamoto T. Differences in clinical course between dementia with Lewy bodies and Alzheimer's disease. *Eur J Neurol* 2009; **16**(2): 212-7.
57. Zweig YR, Galvin JE. Lewy body dementia: the impact on patients and caregivers. *Alzheimers Res Ther* 2014; **6**(2): 21.
58. Morandi A, Davis D, Bellelli G, et al. The Diagnosis of Delirium Superimposed on Dementia: An Emerging Challenge. *J Am Med Dir Assoc* 2017; **18**(1): 12-8.
59. Vardy E, Holt R, Gerhard A, Richardson A, Snowden J, Neary D. History of a suspected delirium is more common in dementia with Lewy bodies than Alzheimer's disease: a retrospective study. *Int J Geriatr Psychiatry* 2014; **29**(2): 178-81.
60. Jicha GA, Schmitt FA, Abner E, et al. Prodromal clinical manifestations of neuropathologically confirmed Lewy body disease. *Neurobiol Aging* 2010; **31**(10): 1805-13.
61. Andersen CK, Lauridsen J, Andersen K, Kragh-Sorensen P. Cost of dementia: impact of disease progression estimated in longitudinal data. *Scand J Public Health* 2003; **31**(2): 119-25.
62. Bharmal MF, Dedhiya S, Craig BA, et al. Incremental dementia-related expenditures in a medicaid population. *Am J Geriatr Psychiatry* 2012; **20**(1): 73-83.
63. Zhu CW, Scarmeas N, Stavitsky K, et al. Comparison of costs of care between patients with Alzheimer's disease and dementia with Lewy bodies. *Alzheimers Dement* 2008; **4**(4): 280-4.
64. Vossius C, Rongve A, Testad I, Wimo A, Aarsland D. The use and costs of formal care in newly diagnosed dementia: a three-year prospective follow-up study. *Am J Geriatr Psychiatry* 2014; **22**(4): 381-8.
65. Banerjee S, Samsi K, Petrie CD, et al. What do we know about quality of life in dementia? A review of the emerging evidence on the predictive and explanatory value of disease specific measures of health related quality of life in people with dementia. *Int J Geriatr Psychiatry* 2009; **24**(1): 15-24.
66. Ready RE, Ott BR, Grace J. Insight and cognitive impairment: effects on quality-of-life reports from mild cognitive impairment and Alzheimer's disease patients. *Am J Alzheimers Dis Other Demen* 2006; **21**(4): 242-8.
67. Sands LP, Ferreira P, Stewart AL, Brod M, Yaffe K. What explains differences between dementia patients' and their caregivers' ratings of patients' quality of life? *Am J Geriatr Psychiatry* 2004; **12**(3): 272-80.
68. Bostrom F, Jonsson L, Minthon L, Londos E. Patients with dementia with lewy bodies have more impaired quality of life than patients with Alzheimer disease. *Alzheimer Dis Assoc Disord* 2007; **21**(2): 150-4.
69. EuroQolGroup. EuroQol—a new facility for the measurement of health related quality of life. *Health Policy (New York)* 1990; **16**: 199-208.
70. Dolan P. Modeling valuations for EuroQol health states. *Med Care* 1997; **35**(11): 1095-108.

71. Larsson V, Engedal K, Aarsland D, Wattmo C, Minthon L, Londos E. Quality of life and the effect of memantine in dementia with lewy bodies and Parkinson's disease dementia. *Dement Geriatr Cogn Disord* 2011; **32**(4): 227-34.
72. Donaldson C, Tarrrier N, Burns A. Determinants of carer stress in Alzheimer's disease. *Int J Geriatr Psychiatry* 1998; **13**(4): 248-56.
73. Huang SS, Lee MC, Liao YC, Wang WF, Lai TJ. Caregiver burden associated with behavioral and psychological symptoms of dementia (BPSD) in Taiwanese elderly. *Arch Gerontol Geriatr* 2012; **55**(1): 55-9.
74. Lee DR, McKeith I, Mosimann U, Ghosh-Nodyal A, Thomas AJ. Examining carer stress in dementia: the role of subtype diagnosis and neuropsychiatric symptoms. *Int J Geriatr Psychiatry* 2013; **28**(2): 135-41.
75. Ricci M, Guidoni SV, Sepe-Monti M, et al. Clinical findings, functional abilities and caregiver distress in the early stage of dementia with Lewy bodies (DLB) and Alzheimer's disease (AD). *Arch Gerontol Geriatr* 2009; **49**(2): e101-4.
76. Svendsboe E, Terum T, Testad I, et al. Caregiver burden in family carers of people with dementia with Lewy bodies and Alzheimer's disease. *Int J Geriatr Psychiatry* 2016; **31**(9): 1075-83.
77. Chwiszczuk L, Breivte M, Hynninen M, Gjerstad MD, Aarsland D, Rongve A. Higher Frequency and Complexity of Sleep Disturbances in Dementia with Lewy Bodies as Compared to Alzheimer's Disease. *Neurodegener Dis* 2016; **16**(3-4): 152-60.
78. Galvin JE, Duda JE, Kaufer DI, Lippa CF, Taylor A, Zarit SH. Lewy body dementia: caregiver burden and unmet needs. *Alzheimer Dis Assoc Disord* 2010; **24**(2): 177-81.
79. Killen A, Flynn D, De Brun A, et al. Support and information needs following a diagnosis of dementia with Lewy bodies. *Int Psychogeriatr* 2016; **28**(3): 495-501.